SOLID PREPARATION CONTAINING SINGLE CRYSTAL FORM

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TECHNICAL FIELD

The present invention relates to a solid preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid for oral administration. More particularly, it relates to a solid preparation comprising 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid as a single crystal form, and a method for producing the same.

BACKGROUND ART

2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid has a strong activity for inhibiting xanthine oxidase or a uric acid decreasing action, and it is expected to be a therapeutic agent for gout or hyperuricemia, as has been described in International Publication WO92/09279.

In International Publication WO99/65885, there are described following six crystal polymorphs of 2-(3-cyano-4-isobutyloxyphehyl)-4-methyl-5-thiazole carboxylic acid, i.e., a polymorph which shows an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of about 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70° (crystal A).;

a polymorph which has specific peaks at a reflection angle 2θ of about 6.76°, 8.08°, 9.74°, 11.50°, 12.22°, 13.56°, 15.76°, 16.20°, 17.32°, 19.38°, 21.14°, 21.56°, 23.16°, 24.78°, 25.14°, 25.72°, 26.12°, 26.68°, 27.68° and 29.36° (crystal B);

a polymorph which has specific peaks at a reflection angle 2θ of about 6.62°, 10.82°, 13.36°, 15.52°, 16.74°, 17.40°, 18.00°, 18.70°, 20.16°, 20.62°, 21.90°, 23.50°, 24.78°, 25.18°, 34.08°, 36.72° and 38.04° (crystal C);

a polymorph which has specific peaks at a reflection angle 2θ of about 8.32°, 9.68°, 12.92°, 16.06°, 17.34°, 19.38°, 21.56°, 24.06°, 26.00°, 30.06°, 33.60° and 40.34° (crystal D).; and

a polymorph which has specific peaks at a reflection angle 2θ of about 6.86°, 8.36°, 9.60°, 11.76°, 13.74°, 14.60°, 15.94°, 16.74°, 17.56°, 20.00°, 21.26°, 23.72°, 24.78°, 25.14°, 25.74°, 26.06°, 26.64°, 27.92°, 28.60°, 29.66° and 29.98° (crystal G), and an amorphous (also referred to as crystal E).

In said International Publication WO99/65885, it is described that crystals A, C and G are useful in view of retention of a crystal form in long term storage. Among them, crystal A is preferred in view of industrial superiority.

However, the publication is silent about what the industrial superiority means. Further, the publication has no evidence (data) supporting the fact that the crystal A is preferred in view of industrial superiority.

The present inventors investigated this matter and found that, in formulating 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid, it is not possible to obtain preparations having no variation in the dissolution profiles of drugs, even if such a crystal form is used as is thought to be most stable in a physical stability test. Further, they found that there is a crystal form that is suitable for preparing preparations, independently from the characteristics of the crystals (including amorphous) of drug substances and have reached the invention.

An object of the invention is, therefore, to provide solid preparations of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid which is stable and which is little variation in the dissolution profiles.

DISCLOSURE OF THE INVENTION

The invention provides solid preparations containing a single crystal form of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, excipients and disintegrating agents.

Further, the invention provides a process for producing solid preparations containing a single crystal form of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, excipients and disintegrating agents.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an X-ray powder diffraction pattern showing the transformation of crystal B in Reference Example 1.

FIG. **2** is an X-ray powder diffraction pattern showing the transformation of crystal D in Reference Example 1.

FIG. **3** is an X-ray powder diffraction pattern showing the transformation of crystal E in Reference Example 1.

FIG. **4** is a data showing the transformation speed of crystal B in Reference Example 1 (unsealed state at 40° C./75% RH).

FIG. **5** is a data showing the transformation speed of crystal D in Reference Example 1 (unsealed at 40° C./75% RH).

FIG. **6** is a data showing the transformation speed of crystal E in Reference example 1 (unsealed at 40° C./75% RH).

FIG. **7** shows dissolution profiles of tablets containing crystal A (particles 1 to 4) in Example 4 each having a different average particle size.

BEST MODE FOR CARRYING OUT THE INVENTION

The single crystal of the 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid (also referred to as the drug substance of the invention) of the invention is that which has a characteristic spectrum when the drug substance is analyzed by a solid NMR or that having specific peaks when analyzed by an X-ray powder diffraction.

The crystal of the invention, i.e., the crystal A of the drug substance of the invention has, when analyzed by a solid ^{15}N-NMR a, a spectrum having specific signals at 226 ppm, 228 ppm, 276 ppm, and 282 ppm. When analyzed by a solid ^{13}C-NMR, the crystal A has approximately equivalent doublet peak at 20 ppm.

Further, the crystal of the drug substance of the invention shows an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of about 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70°.

The crystal of the drug substance of the invention can be produced by the method shown in, for example, International Publication WO 92/09279 and WO 99/65885.

The crystal of the drug substance of the invention is contained in the solid preparation of the invention preferably in an amount of 1 to 50 parts by weight based on 100 parts by weight of the solid preparation.

There are no particular restrictions to the average particle size of the crystal of the drug substance of the invention contained in the solid preparation of the invention. The